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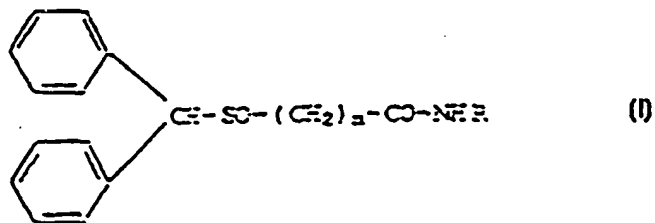
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<p>54) Title: USE OF SULFINYL BENZHYDRYL DERIVATIVES FOR TREATING DRUG-INDUCED SLEEPINESS</p>	

THE UNITED STATES OF AMERICA  
DEPARTMENT OF COMMERCE  
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**(57) Abstract**

The invention concerns the use for making medicines with waking effect in conditions of disorders affecting wakefulness related to morphine treatment, of sulphinyl benzhydryl compounds of formula (I) in which: each of the cycles is substituted by one or several groups F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, methylenedioxy; R is -OH, H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or R<sub>1</sub>R<sub>2</sub>N-Y-, where Y is a hydrocarbon radical in C<sub>1</sub>-C<sub>4</sub> with linear or branched chain; n is a whole number equal to 1, 2 or 3; and their additive salts when R comprises a basic radical. Said medicines enable to reduce sleepiness in patients without affecting the antalgic effect of morphine.

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## **USE OF SULFINYL BENZHYDRYL DERIVATIVES FOR TREATING DRUG-RELATED SLEEPINESS**

The object of the invention is a new therapeutic utilization of sulfinyl benzhydryl derivatives.

More specifically, it is concerned with the utilization of such derivatives in situations with problems with wakefulness related to an analgesic treatment as applied in severe pathologies, such as cancer or for the sequelae of severe painful diseases.

Approximately 40% of cancer patients have to face pain during the evolution of their disease.

This occurs either because of the unfavorable progression of the cancer or because of sequelae of the various treatments employed.

A few years ago, the World Health Organization established a number of principles for the treatment of pain in oncology. Notably, it considered that morphine should occupy an important place in this treatment.

Due to this impetus, and in spite of the cultural prejudices relating to morphine, this product is now prescribed and accepted more and more easily.

While its great efficacy on the analgesic level does not need to be demonstrated any longer, one cannot keep quiet about its side effects, in particular, the sleepiness which it causes. The various studies, which evaluated it, report that 30 to 50% of patients on morphine are bothered by this when they take it within the framework of the chronic treatment of cancer.

The present progress of research in the treatment of pain is mostly oriented toward the perspective of decreasing these side effects, particularly sleepiness.

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The products which the clinician has available today are essentially amphetamine derivatives. However, these derivatives have major disadvantages, related to their adverse cardiovascular and neuropsychological effects on the one hand and dependence during long-term usage on the other hand.

When searching for a solution to this problem, the inventors turned to the evaluation of the effect of known compounds in a context of morphine treatment based on their waking effect and on their ability to stimulate wakefulness.

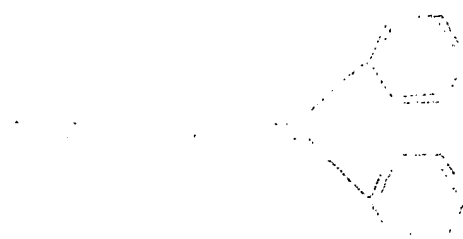
Thus, they were able to verify that, unexpectedly, such compounds antagonize selectively the hypnogenic effect of morphine, without affecting its analgesic activity and without creating any other drawbacks.

It was also verified that these selective antagonistic effects are also manifested toward the somnolence states induced by drugs classically administered with morphine, such as analgesics, antidepressants and anxiolytic agents.

Therefore, the invention has the aim of producing drugs, of compounds capable of having a wakening effect in situations with problems of wakefulness related to a morphine treatment (this expression involving the utilization of morphine or of drugs currently used in this context, as the case may be).

It is also aimed at new pharmaceutical presentations that permit one to obtain, in combination, all the desired effects.

According to the invention, for the production of such drugs, sulfinyl benzhydryl compounds are used which have general formula (I),



Chemical structure of a biphenyl derivative, specifically 1,1'-diphenyl-1,1'-diphenylmethane, showing two phenyl rings connected by a central carbon atom.

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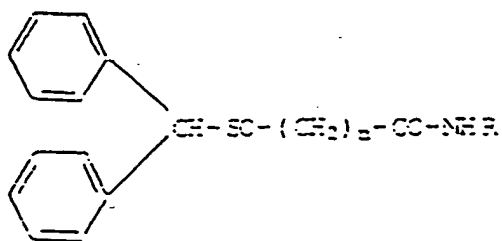
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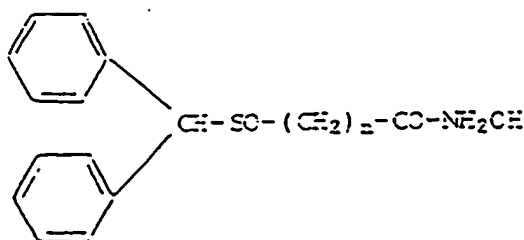


in which,

- each of the rings may be substituted by one or several F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, methylenedioxy groups;
- R represents a hydroxyl group, a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl group or an R<sub>1</sub>R<sub>2</sub>N-Y- group, where Y is a C<sub>1</sub>-C<sub>4</sub> hydrocarbon group with a linear or branched chain;
- n is an integer equal to 1, 2 or 3; and their addition salts when R has a basic group.

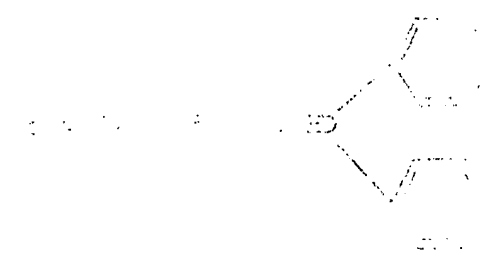
Preferably, R represents an -OH group or a hydrogen atom.

In particular, the invention is aimed at the utilization of sulfinyl benzhydryl acetohydroxamic acid having formula (II),



called adrafinil according to the international name and marketed under the trademark Olmifon®.

More especially, it is aimed at the utilization of its metabolite, namely, sulfinyl benzhydryl acetamide having the formula (III),



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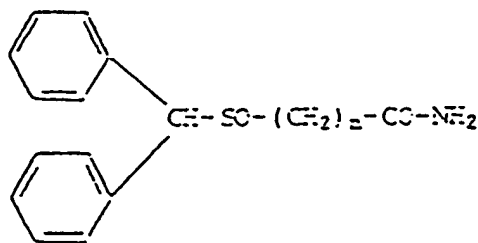
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which has the common international name modafinil and is marketed under the brand name Modiodal®.

The compounds used according to the invention are known for their selective activity for stimulating awakening and wakefulness and are widely used for the treatment of narcolepsy and idiopathic hypersomnia.

Surprisingly, when used in the context of a morphine treatment, as the case may be, combining it with the administration of antidepressants and/or anxiolytic and/or analgesic drugs, they permit a considerable reduction of the state of sleepiness evaluated according to the Epworth scale, while assuring maintenance of the analgesic properties of morphine and those of antidepressant, anxiolytic and analgesic drugs. Thus the patient is returned to a life with satisfactory relationships.

According to an advantageous embodiment of the invention, the said drugs contain at least one compound having formula (I) in an amount of 50 to 600 mg, preferably 100 to 300 mg.

During the manufacture of the drugs, the active ingredients are mixed with pharmaceutically acceptable vehicles for the chosen mode of administration.

Thus, for oral administration, the drugs are prepared in the form of gelcaps, tablets, coated tablets, capsules and analogous forms.

For administration by the injectable route, the drugs are in the form of solutions in injectable ampules.

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8. The eighth part of the document is a list of the names of the persons who have been named in the complaint. The names are listed in alphabetical order of their last names.

One can also use transcutaneous administration in the form of a patch.

As explained in the examples, very favorable results were obtained in clinical application, with the administration of approximately 200 to 400 mg of Modiodal® per day in 1 or 2 intakes, and approximately 1200 to 1800 mg of Olmifon® per day in 2 intakes.

According to another aspect of utilization of the effects resulting from the combined administration of analgesics and/or antidepressants and/or anxiolytic agents on the one hand, and the product that stimulates wakefulness on the other hand, the invention provides a pharmaceutical presentation characterized by the fact that it contains, respectively, the two types of drugs, with an appropriate package insert.

In this presentation, the drugs are in galenic forms, which are appropriate for the chosen route of administration.

In order to illustrate the invention, but without limiting its scope, the results of observations on patients carried out in a confidential manner, within a hospital stay, are reported below. The consent of the patients was obtained after they were explained the measured modes of the prescription.

#### Case No. 1

Mrs. M., born in 1937, is suffering from breast cancer on the right side since 1991. After having undergone a local surgical and radiotherapy treatment, she presented in 1993 the first pain that indicated metastatic spreading to the bones.

Chemotherapy treatment was initiated immediately.

These first painful difficulties led her to a consultation for the pain, where a morphine treatment was initiated rapidly. This provided relief but caused a high degree of sleepiness which went all the way to limit or even stop the prescription at the request of the patient. Between 1994 and 1997, Mrs. M. was regularly followed in consultation for the pain.

1. The present invention relates to a method of determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space.

2. The method of the present invention is particularly useful for determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space.

3. The method of the present invention is particularly useful for determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space.

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4. The method of the present invention is particularly useful for determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space.

5. The method of the present invention is particularly useful for determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space.

6. The method of the present invention is particularly useful for determining the relative positions of two or more points in a three-dimensional space. The method is particularly useful for determining the relative positions of two or more points in a three-dimensional space.



The morphine treatment was started again several times because of the occurrence of the painful episodes related to the appearance of new metastatic centers in the bones and then stopped again when the radiotherapy treatment, which was then initiated, became effective.

Starting from January 1996, the morphine treatment could no longer be interrupted. Its efficacy was moderated by the limitation of the progression of dosage because of the sleepiness that it caused.

Facing the progression of the painful phenomena, at the end of October 1997, the patient was hospitalized. At that time, the dosage of Moscontin® was 100 mg twice every 24 hours, her EVA score was 60, while sleepiness, evaluated on the Epworth scale, was 20. An increase of Moscontin® to 160 mg twice per 24 hours was initiated. After stabilization of the analgesic level to an EVA score of 30, treatment with Modiodal® was initiated at the beginning at a dosage of 100 mg, but then increased rapidly to 200 mg. This dosage permitted the Epworth score to drop to below 10. This degree of wakefulness permitted the patient to take up family relationships of better quality. The efficacy of the analgesia and her better level of wakefulness made it possible for her to go for walks with accompaniment. It should also be pointed out that, in this patient, increased food intake resulted in a weight gain of 2 kg in 10 days.

## Case No. 2

Mrs. B., born in 1952, was suffering from breast cancer since 1987.

This metastasized to the lung, liver and bones.

In September 1997, very disabling costal pain appeared on the right side, which led the patient to go to consultation for pain. Together with flashes of radiotherapy, an analgesic treatment was begun, which was based on a combination of dextropropoxyphene, paracetamol and clonazepam. The patient has already taken oral morphine during the course of her disease and rejected this product because of its effect of causing sleepiness. She desired to continue to exercise her profession. However, because of the persistence of painful phenomena, going to oral morphine proved to be obligatory. The treatment was done with Skenan®, at a dose of 30 mg twice per 24 hours. The patient was seen again after 48 hours.

[illegible]

1. The first step in the process of the investigation is to identify the problem. This is done by the investigator who is responsible for the investigation. The investigator will then gather information about the problem and the people involved. This information will be used to determine the cause of the problem and to develop a plan to solve it. The investigator will then implement the plan and monitor the results. If the problem is not solved, the investigator will go back to the first step and start over.

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She evaluated her pain at 30 on the EVA scale, but was very sleepy. She did not desire to increase the morphine dose. Seven days later, the patient came to consultation again and the rate of the pain was 60 and her state of sleepiness varied significantly, near 16 on the Epworth scale. Hospitalization was accepted with the purpose of equilibrating the pain and somnolence.

The doses of Skenan® were doubled at first and was immediately combined with 200 mg of Modiadal® [spelled Modiodal before]. The result was favorable rapidly, both on the level of pain (EVA 20) as well as on the level of wakefulness (grade lower than 10). Upon leaving the hospital, Mrs. B. was able to take up her professional activities again.

### Case No. 3

Mr. L., born in 1922, has been treated since 1994 for prostate cancer. In July 1997, localization in the cervical vertebrae was revealed based on signs of medullar compression. Laminectomy was practiced first, followed by radiotherapy. These treatments were able to stabilize the neurological lesions. However, Mr. L. still had cervical pain which led to the initiation of an analgesic treatment with slow-release oral morphine. This treatment, which consisted in the administration of Moscontin® at a rate of 30 mg twice per 24 hours, was poorly tolerated, both from the digestive point of view (nausea) and cognitive point of view (significant disorientation). At first hospitalization was proposed. This permitted initiation of a treatment with subcutaneous morphine continuously with an electric syringe in combination with clonazepam given orally. The patient left the hospital, with the grading of his pain on an EVA scale of 30. However, significant sleepiness persisted.

On the vertebral level, the signs of neurological compression reappeared progressively. Since care became difficult at home, Mr. L. was hospitalized again in mid-October. Upon arrival to the hospital, his cervical pain level was always controlled by a moderate dose of morphine (40 mg) administered subcutaneously. However, he exhibited a major state of sleepiness which prevented any dialog with his family (20 on the Epworth scale). Treatment with Modiodal®, 100 mg, and then 200 mg, permitted him to recover a state of wakefulness which had a grade clearly greater than 12.

1. The first step in the process of the investigation is the identification of the problem. This is done by the investigator, who is usually a member of the research team. The investigator will identify the problem by looking at the data and trying to find out what is going on.

2. The second step is to define the problem. This is done by the investigator, who will define the problem in terms of the research question. The research question is a statement that describes the problem and the investigator's goal.

3. The third step is to design the study. This is done by the investigator, who will design the study in terms of the research question. The study design is a plan that describes how the investigator will collect and analyze the data.

4. The fourth step is to collect the data. This is done by the investigator, who will collect the data in terms of the research question. The data collection is the process of gathering information about the problem.

5. The fifth step is to analyze the data. This is done by the investigator, who will analyze the data in terms of the research question. The data analysis is the process of looking at the data and trying to find out what is going on.

6. The sixth step is to interpret the results. This is done by the investigator, who will interpret the results in terms of the research question. The interpretation is the process of looking at the results and trying to find out what they mean.

7. The seventh step is to write the report. This is done by the investigator, who will write the report in terms of the research question. The report is a document that describes the problem, the study design, the data collection, the data analysis, and the results.

8. The eighth step is to present the results. This is done by the investigator, who will present the results in terms of the research question. The presentation is the process of showing the results to the research team and the public.

9. The ninth step is to evaluate the study. This is done by the investigator, who will evaluate the study in terms of the research question. The evaluation is the process of looking at the study and trying to find out how well it was done.

10. The tenth step is to publish the results. This is done by the investigator, who will publish the results in terms of the research question. The publication is the process of putting the results in a journal or book.

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Case No. 4

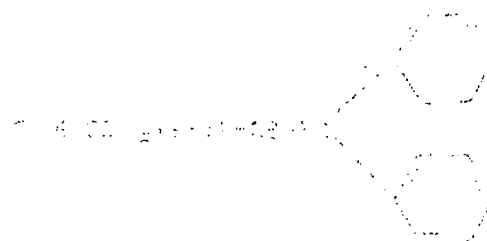
Mrs. Q., born in 1929, had her left eye removed in 1995 because of a melanoma of the choroid after all conservative therapeutic resources were exhausted. In 1997, metastasis in the liver appeared for which a chemotherapy treatment was performed. In the month of October 1997, she came to consultation for vertebral pain graded 60 on the EVA scale. Oral morphine treatment with Moscontin®, 100 mg x 2 permitted stabilization of these painful phenomena (EVA = 40) but at the cost of a disabling state of sleepiness. Hospitalization with the purpose of controlling the problem of sleepiness was accepted by the patient. A treatment with modafinil, at a dose of 300 mg, permitted progressive improvement, namely going from a sleepiness index of 23 to 11.

Case No. 5

Mrs. B., born in 1911, was followed for breast cancer. Metastatic development occurred in the bones. She had a cotyloidien metastasis which was very painful and prevented any movement of the hips. Radiotherapy could not control the pain problem. A morphine treatment was initiated at home, which very quickly resulted in severe sleepiness, making it impossible to care for her at home. Analgesia was not obtained correctly (EVA = 40). Hospitalization permitted control of the pain problem by using subcutaneous morphine at a rate of 40 mg (equivalent dose greater than the dose that she took orally), as well as the sleepiness with a dose of 200 mg of modafinil per day (the sleepiness index went from 22 to 15).

These experimental cases show the efficacy of modafinil on morphine-induced sleepiness and even on that associated with clonazepam.

Thus, the invention provides a means to activate the wakefulness structures of a patient on morphine treatment causing a state of sleepiness, without any effect on the peripheral system. In particular, the invention permits, at least partially or even totally, a return to a normal physical condition for a patient suffering from cancer or of painful sequelae of severe diseases. It also permits an increase of the tolerance to morphine.

[illegible]

1. *How much time do you spend on the Internet each week?*

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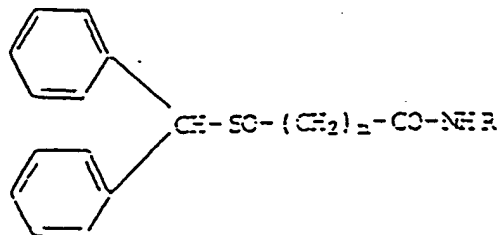
1. *Journal of the American Medical Association*, 1997; 277: 1033-1036.

[illegible]

1. The first step is to identify the problem or question that needs to be answered. This involves understanding the context and the specific requirements of the task.

## PATENT CLAIMS

1. Utilization for the manufacture of drugs with a wakefulness effect in situations of problems with wakefulness related to a morphine treatment, of sulfinyl benzhydryl compounds corresponding to the general formula (I),



in which,

- each of the rings may be substituted by one or several F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, methylenedioxy;
- R represents a hydroxyl group, a hydrogen atom, a C<sub>1</sub>-C<sub>4</sub> alkyl group, a C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl group or an R<sub>1</sub>R<sub>2</sub>N-Y- group, where Y is a C<sub>1</sub>-C<sub>4</sub> hydrocarbon group with a linear or branched chain;
- n is an integer equal to 1, 2 or 3; and their addition salts when R carries a basic group.

2. Utilization according to Claim 1, characterized by the fact that R represents an -OH group or a hydrogen atom.

3. Utilization according to Claim 2, characterized by the fact that the sulfinyl benzhydryl compound is sulfinyl benzhydryl acetohydroxamic acid having formula (II),

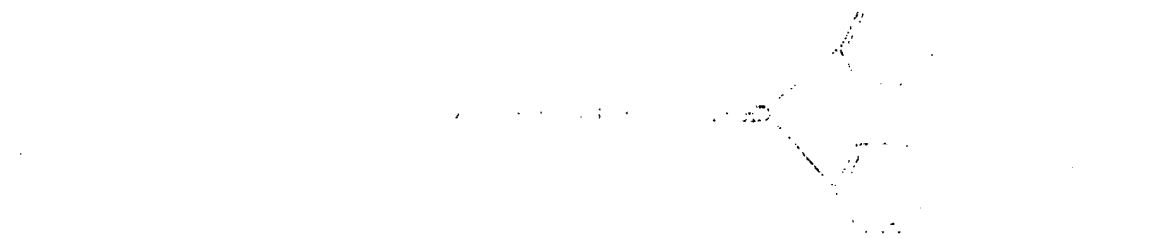


FIG. 1 is a perspective view of the device in its open position, showing the main body 1, the handle 2, and the latch 3.



FIG. 2 is a perspective view of the device in its closed position, showing the main body 1, the handle 2, and the latch 3. The device is shown in a closed position, with the handle 2 folded against the main body 1.

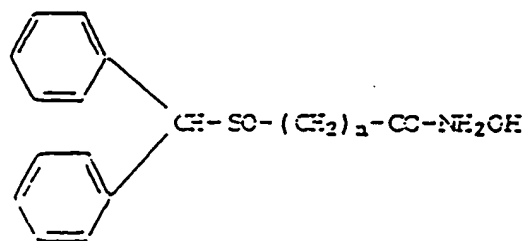
FIG. 3 is a perspective view of the device in its open position, showing the main body 1, the handle 2, and the latch 3. The device is shown in an open position, with the handle 2 extended from the main body 1.

FIG. 4 is a perspective view of the device in its open position, showing the main body 1, the handle 2, and the latch 3. The device is shown in an open position, with the handle 2 extended from the main body 1.

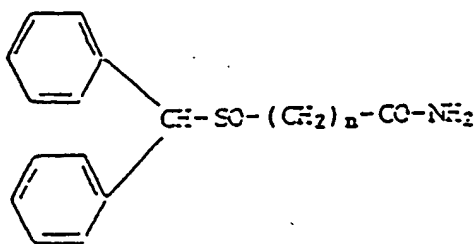
FIG. 5 is a perspective view of the device in its open position, showing the main body 1, the handle 2, and the latch 3. The device is shown in an open position, with the handle 2 extended from the main body 1.

FIG. 6 is a perspective view of the device in its open position, showing the main body 1, the handle 2, and the latch 3. The device is shown in an open position, with the handle 2 extended from the main body 1.





4. Utilization according to Claim 2, characterized by the fact that the sulfinyl benzhydryl compound is sulfinyl benzhydryl acetamide having the formula (III),



5. Utilization according to any of Claims 1 to 4, characterized by the fact that the said drugs contain sulfinyl benzhydryl compounds at a rate from 50 to 600 mg, preferably from 100 to 300 mg.

6. Utilization according to Claim 5, characterized by the fact that the drugs are prepared for oral administration in the form of gelcaps, tablets, coated tablets or capsules.

7. Utilization according to Claim 5, characterized by the fact that the drugs are prepared for administration by injection, in the form of solutions in injectable ampules.

8. Utilization according to Claim 5, characterized by the fact that the drugs are prepared for transcutaneous administration in the form of a patch.

9. Pharmaceutical presentations, characterized by the fact that they contain analgesic and/or antidepressant and/or anxiolytic drugs on the one hand and drugs with a wakefulness-stimulating effect on the other hand, with a package insert.

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## INTERNATIONAL SEARCH REPORT

 Internat. Application No.  
PCT/FR 98/02478

1084

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROTH T. ET AL: "Etiologies and sequelae of excessive daytime sleepiness" CLINICAL THERAPEUTICS, 1996, 18/4 (562-576), XP002075153 USA	1,2,4
Y	see page 562, left-hand column, line 23 - right-hand column, line 8 see page 570, left-hand column, line 30-38 * page 571, table * --- -/--	5-8

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

26 February 1999

Date of mailing of the international search report

15/03/1999

Name and mailing address of the ISA

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Mair, J

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APR 12 1977  
(21MA)

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# INTERNATIONAL SEARCH REPORT

Interr 1st Application No  
PCT/FR 98/02478

1084

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAMBERT F A ET AL: "PSYCHOPHARMACOLOGICAL STUDIES WITH ADRAFINIL A UNIQUE BEHAVIORAL PROFILE IN MICE" J PHARMACOL (PARIS), 17 (1). 1986. 37-52., XP002075154	1-3
Y	see abstract see page 43, right-hand column, line 4-13 see page 44; figure 6 ---	5-8
X	GB 1 584 462 A (LABARATOIRE L. LAFON) 11 February 1981	9
Y	see the whole document ---	5-8
X	"British National Formulary" 1986, THE PHARMACEUTICAL PRESS, LONDON XP002094890 11 see page 156 see page 166 -----	9

1. The present invention relates to a method of determining the similarity of two documents. The method involves comparing the documents on a word-by-word basis and determining the percentage of words that are identical. The percentage of identical words is then used to determine the similarity of the documents.

2. The method of the present invention is particularly useful for determining the similarity of documents in a large database. The method involves comparing the documents on a word-by-word basis and determining the percentage of words that are identical. The percentage of identical words is then used to determine the similarity of the documents.

3. The method of the present invention is particularly useful for determining the similarity of documents in a large database. The method involves comparing the documents on a word-by-word basis and determining the percentage of words that are identical. The percentage of identical words is then used to determine the similarity of the documents.

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4. The method of the present invention is particularly useful for determining the similarity of documents in a large database. The method involves comparing the documents on a word-by-word basis and determining the percentage of words that are identical. The percentage of identical words is then used to determine the similarity of the documents.

5. The method of the present invention is particularly useful for determining the similarity of documents in a large database. The method involves comparing the documents on a word-by-word basis and determining the percentage of words that are identical. The percentage of identical words is then used to determine the similarity of the documents.

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/ FR 98/ 02478

1084

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
see supplementary sheet CONTINUATION OF INFORMATION PCT/ ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

ARTICLE 17

Page 1 of 1

The following text is a translation of the original text into English. It is not a legal translation and should not be used for legal purposes. The original text is in Chinese and is a translation of the original text into English. It is not a legal translation and should not be used for legal purposes.

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1084

see supplementary sheet CONTINUATION OF INFORMATION PCT/ISA/210

Claims partially searched: 1, 2, 5-8

Owing to the large number of compounds defining the general formula of Claim 1 theoretically, the search had to be limited for economic reasons. The search was restricted to the compounds mentioned in the claims and for which pharmacological data are mentioned and to the general concept of the application.

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# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/FR 98/02478

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1584462 A	11-02-1981	BE 865468 A	02-10-1978
		CA 1091679 A	16-12-1980
		CH 628026 A	15-02-1982
		DE 2809625 A	05-10-1978
		DK 140878 A,B,	01-10-1978
		FR 2385693 A	27-10-1978
		IE 46566 B	27-07-1983
		JP 1400453 C	28-09-1987
		JP 53121724 A	24-10-1978
		JP 62009103 B	26-02-1987
		LU 79335 A	28-09-1978
		LU 90153 A	16-02-1998
		NL 7803432 A,C	03-10-1978
		US 4177290 A	04-12-1979

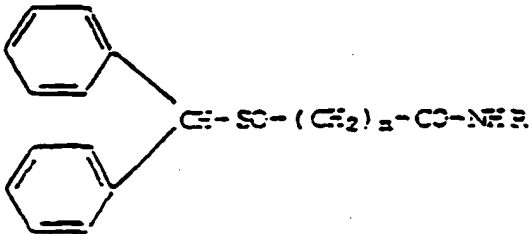
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## DEMANDE INTERNATIONALE PUBLIÉE EN VERTU DU TRAITE DE COOPERATION EN MATIÈRE DE BREVETS (PCT)

(51) Classification internationale des brevets <sup>6</sup> : <b>A61K 31/165</b>	<b>A1</b>	(11) Numéro de publication internationale: <b>WO 99/25329</b> (43) Date de publication internationale: 27 mai 1999 (27.05.99)
<p>(21) Numéro de la demande internationale: PCT/FR98/02478</p> <p>(22) Date de dépôt international: 19 novembre 1998 (19.11.98)</p> <p>(30) Données relatives à la priorité: 97/14519 19 novembre 1997 (19.11.97) FR</p> <p>(71) Déposant (pour tous les Etats désignés sauf US): INSTITUT CURIE [FR/FR]; 26, rue d'Ulm, F-75248 Paris Cedex 05 (FR).</p> <p>(72) Inventeurs; et (75) Inventeurs/Déposants (US seulement): ESTEVE, Marc [FR/FR]; 17, avenue de la Libération, F-94100 Saint-Maur des Fosses (FR). GERTNER, Jacques [FR/FR]; 25, rue de l'Ouest, F-75014 Paris (FR).</p> <p>(74) Mandataires: PEAUCELLE, Chantal etc.; Cabinet Armengaud Aîné, 3, avenue Bugeaud, F-75116 Paris (FR).</p>		<p>(81) Etats désignés: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, brevet ARIPO (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p><b>Publiée</b> <i>Avec rapport de recherche internationale. Avant l'expiration du délai prévu pour la modification des revendications, sera republiée si des modifications sont reçues.</i></p>
<p>(54) Title: USE OF SULPHINYL BENZHYDRYL DERIVATIVES FOR TREATING DRUG-INDUCED SLEEPINESS</p> <p>(54) Titre: UTILISATION DE DERIVES DE BENZHYDRYL SULFINYLE POUR TRAITER LA SOMNOLENCE D'ORIGINE MEDICAMENTEUSE</p>		
<div style="text-align: center;">  <p>(I)</p> </div>		
<p>(57) Abstract</p> <p>The invention concerns the use for making medicines with waking effect in conditions of disorders affecting wakefulness related to morphine treatment, of sulphinyl benzhydryl compounds of formula (I) in which: each of the cycles is substituted by one or several groups F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, methylenedioxy; R is -OH, H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> hydroxyalkyl, or R<sub>1</sub>R<sub>2</sub>N-Y-, where Y is a hydrocarbon radical in C<sub>1</sub>-C<sub>4</sub> with linear or branched chain; n is a whole number equal to 1, 2 or 3; and their additive salts when R comprises a basic radical. Said medicines enable to reduce sleepiness in patients without affecting the antalgic effect of morphine.</p> <p>(57) Abrégé</p> <p>L'invention concerne l'utilisation, pour la fabrication de médicaments à effet d'éveil dans des situations de troubles de la vigilance liés à un traitement morphinique, des composés de benzhydryl sulfinyle de formule (I), dans laquelle, chacun des cycles est substitué par un ou plusieurs groupes F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, alkyle en C<sub>1</sub>-C<sub>4</sub>, alcoxy en C<sub>1</sub>-C<sub>4</sub>, méthylènedioxy; R est -OH, H, alkyle en C<sub>1</sub>-C<sub>4</sub>, hydroxyalkyle en C<sub>1</sub>-C<sub>4</sub>, ou R<sub>1</sub>R<sub>2</sub>N-Y-, où Y est un reste hydrocarboné en C<sub>1</sub>-C<sub>4</sub> à chaîne linéaire ou ramifiée; n est un entier égal à 1, 2 ou 3; et leurs sels d'addition lorsque R comporte un reste basique. Ces médicaments permettent de réduire l'état de somnolence des patients sans affecter l'effet antalgique de la morphine.</p>		

### UNIQUEMENT A TITRE D'INFORMATION

Codes utilisés pour identifier les Etats parties au PCT, sur les pages de couverture des brochures publiant des demandes internationales en vertu du PCT.

AL	Albanie	ES	Espagne	LS	Lesotho	SI	Slovénie
AM	Arménie	FI	Finlande	LT	Lituanie	SK	Slovaquie
AT	Autriche	FR	France	LU	Luxembourg	SN	Sénégal
AU	Australie	GA	Gabon	LV	Lettonie	SZ	Swaziland
AZ	Azerbaïdjan	GB	Royaume-Uni	MC	Monaco	TD	Tchad
BA	Bosnie-Herzégovine	GE	Géorgie	MD	République de Moldova	TG	Togo
BB	Barbade	GH	Ghana	MG	Madagascar	TJ	Tadjikistan
BE	Belgique	GN	Guinée	MK	Ex-République yougoslave de Macédoine	TM	Turkménistan
BF	Burkina Faso	GR	Grèce	ML	Mali	TR	Turquie
BG	Bulgarie	HU	Hongrie	MN	Mongolie	TT	Trinité-et-Tobago
BJ	Bénin	IE	Irlande	MR	Mauritanie	UA	Ukraine
BR	Brésil	IL	Israël	MW	Malawi	UG	Ouganda
BY	Bélarus	IS	Islande	MX	Mexique	US	Etats-Unis d'Amérique
CA	Canada	IT	Italie	NE	Niger	UZ	Ouzbékistan
CF	République centrafricaine	JP	Japon	NL	Pays-Bas	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norvège	YU	Yougoslavie
CH	Suisse	KG	Kirghizistan	NZ	Nouvelle-Zélande	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	République populaire démocratique de Corée	PL	Pologne		
CM	Cameroun	KR	République de Corée	PT	Portugal		
CN	Chine	KZ	Kazakhstan	RO	Roumanie		
CU	Cuba	LC	Sainte-Lucie	RU	Fédération de Russie		
CZ	République tchèque	LI	Liechtenstein	SD	Soudan		
DE	Allemagne	LK	Sri Lanka	SE	Suède		
DK	Danemark	LR	Libéria	SG	Singapour		
EE	Estonie						

## UTILISATION DE DERIVES DE BENZHYDRYL SULFINYLE POUR TRAITER LA SOMNOLENCE D'ORIGINE MEDICAMENTEUSE

5

L'invention a pour objet une nouvelle utilisation en thérapeutique de dérivés de benzhydryl sulfinyle.

Elle concerne, plus spécialement, l'utilisation de tels dérivés dans des situations de troubles de la  
10 vigilance liés à un traitement anti-douleur tel qu'appliqué dans des pathologies lourdes comme le cancer, ou pour les séquelles douloureuses d'affections graves.

40% environ des patients cancéreux ont en effet au cours de l'évolution de leur maladie à faire face à la  
15 douleur.

Celle-ci survient soit du fait de la progression défavorable du cancer, soit du fait de séquelles des différents traitements entrepris.

L'Organisation Mondiale pour la Santé a établi, il y a  
20 plusieurs années, un certain nombre de principes pour la prise en charge de la douleur en cancérologie. Elle a notamment rappelé la place importante que devait tenir la morphine dans ce traitement.

Grâce à cette impulsion, et malgré les préjugés  
25 culturels tournant autour de la morphine, ce produit est maintenant prescrit et accepté de plus en plus facilement.

Si sa grande efficacité sur le plan antalgique n'est plus à démontrer, on ne peut pas passer sous silence ses effets secondaires, en particulier la somnolence qu'elle  
30 provoque. Les différentes études qui l'ont évaluée rapportent qu'elle gêne 30 à 50% des patients sous morphine

lorsque celle-ci est prise dans le cadre d'un traitement chronique du cancer.

Les démarches de recherche actuelles dans le traitement de la douleur sont en majorité orientées vers la perspective de voir diminuer ces effets secondaires, et tout particulièrement la somnolence.

Les produits dont dispose le clinicien à ce jour sont essentiellement des dérivés amphétaminiques. Cependant de tels dérivés sont à l'origine d'inconvénients majeurs, liés à leurs effets cardiovasculaires et neuropsychiques indésirables d'une part, et de dépendance lors de l'usage à long terme, d'autre part.

En recherchant une solution à ce problème, les inventeurs se sont orientés vers l'évaluation des effets, dans un contexte de traitement morphinique, de composés connus pour leur pouvoir éveillant et leur capacité à stimuler la vigilance.

Ils ont pu ainsi vérifier que, de manière inattendue, de tels composés antagonisaient sélectivement l'effet hypnogène de la morphine, sans affecter son activité antalgique, et ce sans créer d'autres inconvénients.

Il a également été vérifié que ces effets antagonistes sélectifs s'exerçaient aussi vis-à-vis des états de somnolence induits par les médicaments classiquement administrés avec la morphine, tels que les antalgiques, anti-dépresseurs et anxyolytiques.

L'invention vise donc l'utilisation, pour la fabrication de médicaments, de composés capables d'exercer un effet éveillant dans des situations de troubles de la vigilance liés à un traitement morphinique (cette expression englobant l'utilisation de morphine ou dérivés

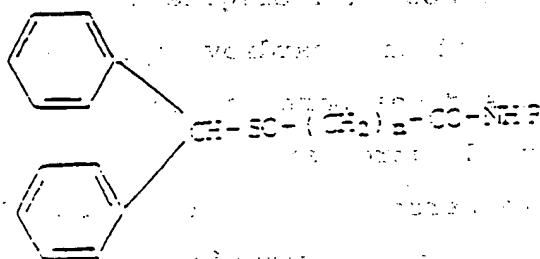


de celle-ci avec le cas échéant, les médicaments couramment utilisés dans ce type de contexte).

Elle vise également de nouvelles présentations pharmaceutiques permettant d'obtenir conjointement l'ensemble des effets recherchés.

Conformément à l'invention, on utilise, pour la fabrication desdits médicaments, des composés de benzhydryl sulfinyle répondant à la formule générale (I),

10



15

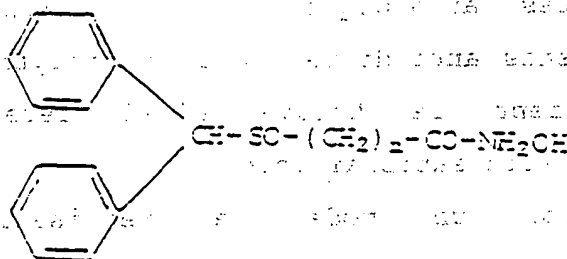
dans laquelle,

- chacun des cycles peut être substitué par un ou plusieurs groupes F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, alkyle en C<sub>1</sub>-C<sub>4</sub>, alkoxy en C<sub>1</sub>-C<sub>4</sub>, méthylènedioxy ;
- R représente un groupe hydroxyle, un atome d'hydrogène, un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, un groupe hydroxyalkyle en C<sub>1</sub>-C<sub>4</sub>, ou un groupe R<sub>1</sub>R<sub>2</sub>N-Y-, où Y est un reste hydrocarboné en C<sub>1</sub>-C<sub>4</sub> à chaîne linéaire ou ramifiée ;
- n est un entier égal à 1, 2 ou 3 ; et leurs sels d'addition lorsque R comporte un reste basique.

De manière préférée, R représente un groupe -OH ou un atome d'hydrogène.

L'invention vise en particulier l'utilisation de l'acide benzhydryl sulfinyl-acétohydroxamique de formule (II),

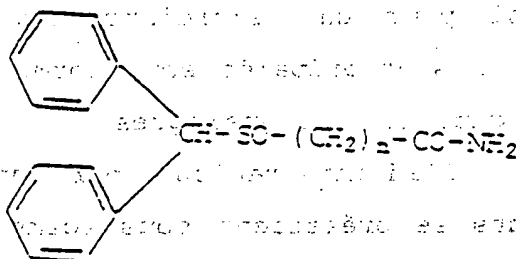
5



désigné par modafinil selon la dénomination comme internationale et commercialisé sous la marque Olmifon®.

10 Elle vise tout spécialement l'utilisation de son métabolite, à savoir le benzhydryl sulfinyl acétamide de formule (III),

15



20 répondant à la dénomination commune internationale de modafinil et commercialisé sous la marque Modiodal®.

Les composés utilisés selon l'invention sont connus pour leur activité sélective de stimulation de l'éveil et de la vigilance et sont largement utilisés pour le 25 traitement de la narcolepsie et de l'hypersomnie idiopathique.

De manière surprenante, utilisés dans le contexte d'un traitement morphinique, associé le cas échéant à l'administration d'anti-dépresseurs et/ou anxiolytiques 30 et/ou antalgiques, ils permettent de réduire considérablement l'état de somnolence, évalué selon

l'échelle Epworth, tout en assurant le maintien des propriétés antalgiques de la morphine et celles des médicaments anti-dépresseurs, anxiolytiques ou antalgiques. Le patient se trouve ainsi rétabli dans une vie relationnelle satisfaisante.

Selon un mode de réalisation avantageux de l'invention, lesdits médicaments renferment au moins un composé de formule (I), à raison de 50 à 600 mg de préférence de 100 à 300 mg.

Lors de l'élaboration des médicaments, les principes actifs sont mélangés avec les véhicules pharmaceutiquement acceptables pour le mode d'administration choisi.

Ainsi pour une administration par voie orale, les médicaments sont préparés sous forme de gélules, comprimés, dragées, capsules, et analogues.

Pour l'administration par voie injectable, les médicaments se présentent sous forme de solutions dans des ampoules injectables.

On peut également avoir recours à une administration par voie transcutanée, sous forme de patch.

Comme exposé dans les exemples, des résultats très favorables ont été obtenus en clinique avec des administrations de 200 à 400 mg environ par jour de Modiodal<sup>®</sup>, en 1 ou 2 prises, et de 1200 à 1800 mg environ par jour d'Olmifon<sup>®</sup> en 2 prises.

Selon un autre aspect mettant à profit les effets résultant de l'administration conjointe d'antalgiques, et/ou d'anti-dépresseurs et/ou anxiolytiques d'une part, et de produits stimulants la vigilance d'autre part, l'invention fournit une présentation pharmaceutique caractérisée en ce qu'elle renferme respectivement les deux

types de médicaments, avec une notice d'information appropriée.

Dans cette présentation, les médicaments sont sous les formes galéniques appropriées pour la voie d'administration choisie.

Afin d'illustrer l'invention, sans toutefois en limiter sa portée, on rapporte ci-après les résultats d'observations effectuées sur des patients, de manière confidentielle, dans le cadre d'une hospitalisation. Le consentement des patients a été obtenu après leur avoir expliqué les modalités compassionnelles de la prescription.

#### CAS N°1

Madame M. née, en 1937, est atteinte d'un cancer du sein droit depuis 1991. Après avoir subi un traitement local chirurgical et radiothérapeutique, elle présente en 1993 les premières douleurs révélatrices d'une diffusion métastatique osseuse.

Un traitement chimiothérapique est immédiatement instauré.

Ces premières difficultés douloureuses la conduisent en consultation sur la douleur, où est initié rapidement un traitement morphinique. Celui-ci la soulage, mais occasionne un degré de somnolence important allant jusqu'à limiter, voire arrêter, sa prescription à la demande de la patiente. Entre 1994 et 1997 Madame M. est régulièrement suivie à la consultation de la douleur.

Le traitement morphinique est repris à plusieurs reprises du fait de la survenue d'épisodes douloureux en rapport avec l'éclosion de nouveaux foyers métastatiques

osseux, puis arrêté lorsque l'efficacité du traitement radiothérapique, alors institué, est obtenu.

A partir de janvier 1996, le traitement morphinique ne pourra plus être interrompu. Son efficacité est modérée du fait de la limitation de sa progression en posologies eu égard à la somnolence qu'il occasionne.

Devant la progression des phénomènes douloureux, fin octobre 1997, la patiente est hospitalisée. A ce moment, la posologie du Moscontin® est à 100 mg deux fois par 24 heures, son score EVA est à 60, sa somnolence évaluée sur l'échelle d'Epworth est à 20. Une augmentation du Moscontin® à 160 mg deux fois par 24 heures est effectuée. Après stabilisation du niveau antalgique à un score EVA de 30, un traitement par Modiodal®, initialement à la posologie de 100 mg puis rapidement à 200 mg est instauré. Cette posologie permet de voir son score d'Epworth chuter au-dessous de 10. Cette qualité d'éveil lui a permis une reprise des relations familiales de meilleure qualité. L'efficacité de l'analgésie et son meilleur niveau de vigilance lui ont rendu possibles des promenades accompagnées. Il est à noter aussi chez cette patiente une reprise alimentaire se traduisant par une prise pondérale de 2 kgs en 10 jours.

## 25 CAS N°2

Madame B. née, en 1952, présente depuis 1987 un cancer du sein.

Son évolution s'est faite sur le mode métastatique aux niveaux pulmonaire, hépatique et osseux.

En septembre 1997, apparaissent des douleurs très invalidantes costales droites qui la conduisent à la consultation de la douleur. Conjointement à des flashes de radiothérapie, est débuté un traitement antalgique qui associe dextropropoxyphène, paracétamol et clonazépam. La patiente a déjà au cours de sa maladie pris de la morphine orale et redoute ce produit du fait de ses effets hypnotiques. Elle souhaite continuer d'exercer son métier. Devant la persistance des phénomènes douloureux le passage à la morphine orale s'avère obligatoire. Le traitement se fait par Skénan<sup>®</sup>, à la dose de 30 mg, deux fois par 24 heures. On revoit au bout de 48 heures la patiente. Elle évalue sa douleur à 30 sur l'échelle EVA, mais se sent très somnolente. Elle ne souhaite pas augmenter la posologie morphinique. Sept jours plus tard la patiente consulte à nouveau, la douleur est cotée à 60 et son état de somnolence est important, coté à 16 sur l'échelle d'Epworth. L'hospitalisation dans le but d'équilibrer douleur et somnolence est acceptée.

Les doses de Skénan<sup>®</sup> sont doublées d'emblée et on leur associe immédiatement 200 mg de Modiadal<sup>®</sup>. Le résultat est rapidement favorable tant sur le plan antalgique (EVA 20) qu'au niveau de la vigilance (cotation inférieure à 10). A la sortie de l'hôpital Madame B. a pu reprendre ses activités professionnelles.

Monsieur L., né en 1922, est traité depuis 1994 pour un cancer de la prostate. En juillet 1997 une localisation vertébrale cervicale se révèle par des signes de compression médullaire. Une laminectomie est pratiquée dans un premier temps suivie d'une radiothérapie. Ces traitements vont permettre de stabiliser les lésions neurologiques. Cependant Monsieur L. va conserver des douleurs cervicales qui amènent à débiter un traitement antalgique par morphine orale à libération prolongée. Ce traitement, consistant à administrer du Moscontin<sup>®</sup>, à raison de 30 mg, deux fois par 24 heures, sera mal supporté tant sur le plan digestif (nausées) que cognitif (désorientation importante). Une première hospitalisation est proposée. Elle permettra la mise en route d'un traitement par morphine sous-cutanée, en continu, à la seringue électrique associé à du Clonazépan par voie orale. Le patient sort de l'hôpital, la cotation de sa douleur sur l'échelle EVA est à 30. Il persiste cependant une somnolence importante.

Sur le plan vertébral, les signes de compression neurologique vont réapparaître progressivement. Les conditions de soin devenant difficiles à domicile, Monsieur L. est réhospitalisé mi-octobre. A l'arrivée en hospitalisation, sa douleur cervicale est toujours contrôlée par une dose modérée de morphine (40 mg) par voie sous-cutanée. Il présente cependant un état de somnolence majeur empêchant tout dialogue suivi avec sa famille. (20 sur l'échelle d'Epworth). Un traitement par Modiodal<sup>®</sup> 100 mg, puis 200 mg, va lui permettre de recouvrir un état de vigilance nettement supérieur côté à 12.

CAS N°4

Madame Q., née en 1929, a été énuclée de l'oeil gauche en 1995 pour un mélanome de la choroïde au-dessus de toute ressource thérapeutique conservatrice. En 1997, apparaissent des métastases hépatiques pour lesquelles un traitement chimiothérapique est effectué. Au mois d'octobre 1997, elle consulte pour des douleurs vertébrales cotées 60 à l'EVA. Un traitement morphinique par voie orale Moscontin® 100 mg x 2 va permettre de stabiliser ces phénomènes douloureux (EVA = 40), mais au prix d'un état de somnolence invalidant. Une hospitalisation dans le but de régler le problème de la somnolence est acceptée par la patiente. Un traitement par modafinil va permettre, à la dose de 300 mg, progressivement obtenue, de voir passer l'index de somnolence de 23 à 11.

CAS N°5

Madame B., née en 1911, est suivie pour un cancer du sein. Son évolution métastatique s'est faite au niveau osseux. Elle présente une métastase sus cotyloïdienne très douloureuse lui empêchant toute mobilité de la hanche. Une radiothérapie n'a pu régler le problème algique. Un traitement morphinique va être instituer à domicile, il va très rapidement entraîner une somnolence forte, rendant les soins à la maison impossibles. L'antalgie n'est pas correctement obtenue (EVA = 40). L'hospitalisation va permettre de régler le problème antalgique en utilisant la morphine par voie sous-cutanée à raison de 40 mg (équivalent-dose supérieur à la dose qu'elle prenait par



voie orale) ainsi que la somnolence, par une dose de 200 mg de modafinil par jour (l'index de somnolence va passer de 22 à 15).

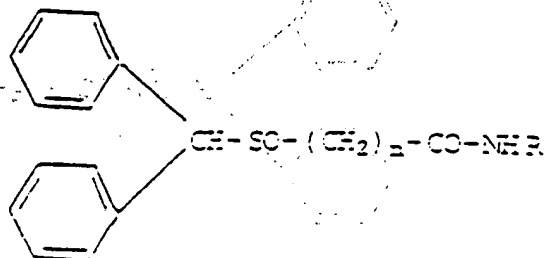
Ces cas pilotes montrent l'efficacité du modafinil sur la somnolence morphinique, voire sur celle associée au clonazépam.

L'invention fournit ainsi des moyens d'activer les structures d'éveil d'un patient sous traitement morphinique entraînant un état de somnolence, sans effet sur le système périphérique. L'invention permet en particulier un retour au moins partiel, voire total, à une condition physique normale pour le patient atteint d'un cancer ou souffrant de séquelles douloureuses d'affections graves. Elle permet également d'augmenter la tolérance à la morphine.

## REVENDEICATIONS

1. Utilisation, pour la fabrication de médicaments à effet d'éveil dans des situations de troubles de la vigilance liés à un traitement morphinique, des composés de benzhydryl sulfinyle répondant à la formule générale (I),

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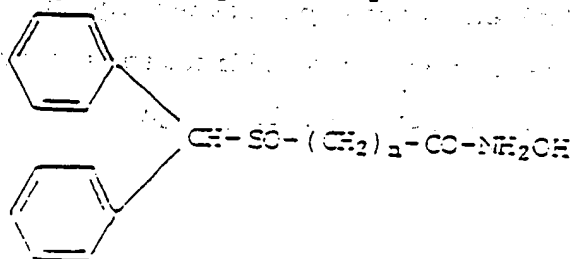
dans laquelle,

- chacun des cycles peut être substitué par un ou plusieurs groupes F, Cl, Br, CF<sub>3</sub>, NO<sub>2</sub>, NH<sub>2</sub>, alkyle en C<sub>1</sub>-C<sub>4</sub>, alkoxy en C<sub>1</sub>-C<sub>4</sub>, méthylènedioxy ;
- R représente un groupe hydroxyle, un atome d'hydrogène, un groupe alkyle en C<sub>1</sub>-C<sub>4</sub>, un groupe hydroxyalkyle en C<sub>1</sub>-C<sub>4</sub>, ou un groupe R<sub>1</sub>R<sub>2</sub>N-Y-, où Y est un reste hydrocarboné en C<sub>1</sub>-C<sub>4</sub> à chaîne linéaire ou ramifiée ;
- n est un entier égal à 1, 2 ou 3 ; et leurs sels d'addition lorsque R comporte un reste basique.

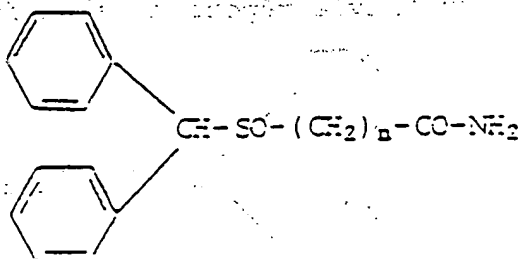
- 2.- Utilisation selon la revendication 1, caractérisée en ce que R représente un groupe -OH ou un atome d'hydrogène.

- 3.- Utilisation selon la revendication 2, caractérisée en ce que le composé de benzhydryl sulfinyle est l'acide benzhydryl sulfinyl-acétohydroxamique de formule (II),

30



4. Utilisation selon la revendication 2, caractérisée en ce que le composé de benzhydryl sulfinyle est le benzhydryl sulfinyl-acétamide de formule (III),



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5. Utilisation selon l'une quelconque des revendications 1 à 4, caractérisée en ce que lesdits médicaments renferment les composés de benzhydryl sulfinyle à raison de 50 à 600 mg, de préférence de 100 à 300 mg.

6. Utilisation selon la revendication 5, caractérisée en ce que les médicaments sont préparés pour une administration par voie orale, sous forme de gélules, comprimés, dragées ou capsules.

- 7.- Utilisation selon la revendication 5, caractérisée en ce que les médicaments sont préparés pour une administration par voie injectable, sous forme de solutions dans des ampoules injectables.

8. Utilisation selon la revendication 5, caractérisée en ce que les médicaments sont préparés pour une administration par voie transcutanée, sous forme de patch.

9. Présentations pharmaceutiques, caractérisées en ce qu'elles renferment des médicaments antalgiques et/ou anti-dépresseurs et/ou anxiolytiques d'une part, et des

médicaments à effet stimulant de la vigilance d'autre part,  
avec une notice d'information.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/FR 98/02478

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/165

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROTH T. ET AL: "Etiologies and sequelae of excessive daytime sleepiness" CLINICAL THERAPEUTICS, 1996, 18/4 (562-576), XP002075153 USA	1,2,4
Y	see page 562, left-hand column, line 23 - right-hand column, line 8 see page 570, left-hand column, line 30-38 * page 571, table * --- -/--	5-8

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

26 February 1999

Date of mailing of the international search report

15/03/1999

Name and mailing address of the ISA

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Authorized officer

Mair, J

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/FR 98/02478

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAMBERT F A ET AL: "PSYCHOPHARMACOLOGICAL STUDIES WITH ADRAFINIL A UNIQUE BEHAVIORAL PROFILE IN MICE" J PHARMACOL (PARIS), 17 (1). 1986. 37-52., XP002075154	1-3
Y	see abstract see page 43, right-hand column, line 4-13 see page 44; figure 6	5-8
X	GB 1 584 462 A (LABORATOIRE L. LAFON) 11 February 1981	9
Y	see the whole document	5-8
X	"British National Formulary" 1986, THE PHARMACEUTICAL PRESS, LONDON XP002094890. 11 see page 156 see page 166	9

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/ FR 98/ 02478

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
see supplementary sheet CONTINUATION OF INFORMATION PCT/ ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Application No.

PCT/FR 98/ 02478

see supplementary sheet CONTINUATION OF INFORMATION PCT/ISA/210

Claims partially searched: 1, 2, 5-8

Owing to the large number of compounds defining the general formula of Claim 1 theoretically, the search had to be limited for economic reasons. The search was restricted to the compounds mentioned in the claims and for which pharmacological data are mentioned and to the general concept of the application.



# INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/FR 98/02478

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1584462 A	11-02-1981	BE 865468 A	02-10-1978
		CA 1091679 A	16-12-1980
		CH 628026 A	15-02-1982
		DE 2809625 A	05-10-1978
		DK 140878 A,B,	01-10-1978
		FR 2385693 A	27-10-1978
		IE 46566 B	27-07-1983
		JP 1400453 C	28-09-1987
		JP 53121724 A	24-10-1978
		JP 62009103 B	26-02-1987
		LU 79335 A	28-09-1978
		LU 90153 A	16-02-1998
		NL 7803432 A,C	03-10-1978
		US 4177290 A	04-12-1979

# RAPPORT DE RECHERCHE INTERNATIONALE

Dem. International No.  
PCT/FR 98/02478

A. CLASSEMENT DE L'OBJET DE LA DEMANDE  
CIB 6 A61K31/165

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée (système de classification suivi des symboles de classement)

CIB 6 A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie *	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	ROTH T. ET AL: "Etiologies and sequelae of excessive daytime sleepiness" CLINICAL THERAPEUTICS, 1996, 18/4 (562-576), XP002075153 USA	1,2,4
Y	voir page 562, colonne de gauche, ligne 23 - colonne de droite, ligne 8 voir page 570, colonne de gauche, ligne 30-38 * page 571, tableau * --- -/--	5-8

☒ Voir la suite du cadre C pour la fin de la liste des documents

☒ Les documents de familles de brevets sont indiqués en annexe

\* Catégories spéciales de documents cités:

- "A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent
- "E" document antérieur, mais publié à la date de dépôt international ou après cette date
- "L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)
- "O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens
- "P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié après la date de dépôt international ou la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive par rapport au document considéré isolément

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier

"&" document qui fait partie de la même famille de brevets

Date à laquelle la recherche internationale a été effectivement achevée

26 février 1999

Date d'expédition du présent rapport de recherche internationale

15/03/1999

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# RAPPORT DE RECHERCHE INTERNATIONALE

Dem: Internationale No

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## C.(suite) DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie	Identification des documents cités, avec le cas échéant, l'indication des passages pertinents	no. des revendications visées
X	RAMBERT F. A. ET AL: "PSYCHOPHARMACOLOGICAL STUDIES WITH ADRAFINIL A UNIQUE BEHAVIORAL PROFILE IN MICE" J PHARMACOL (PARIS), 17 (1). 1986. 37-52., XP002075154	1-3
Y	voir abrégé voir page 43, colonne de droite, ligne 4-13 voir page 44; figure 6	5-8
X	GB 1 584 462 A (LABARATOIRE L. LAFON) 11 février 1981	9
Y	voir le document en entier	5-8
X	"British National Formulary" 1986, THE PHARMACEUTICAL PRESS, LONDON XP002094890 11 voir page 156 voir page 166	9

# RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale n°

PCT/FR 98/02478

## **Cadre I Observations - lorsqu'il a été estimé que certaines revendications ne pouvaient pas faire l'objet d'une recherche (suite du point 1 de la première feuille)**

Conformément à l'article 17.2)a), certaines revendications n'ont pas fait l'objet d'une recherche pour les motifs suivants:

1. ☐ Les revendications n°  
se rapportent à un objet à l'égard duquel l'administration n'est pas tenue de procéder à la recherche, à savoir:
2. ☒ Les revendications n°  
se rapportent à des parties de la demande internationale qui ne remplissent pas suffisamment les conditions prescrites pour qu'une recherche significative puisse être effectuée, en particulier:  
**Voir feuille supplémentaire SUITE DES RENSEIGNEMENTS PCT/ISA/210**
3. ☐ Les revendications n°  
sont des revendications dépendantes et ne sont pas rédigées conformément aux dispositions de la deuxième et de la troisième phrases de la règle 6.4.a).

## **Cadre II Observations - lorsqu'il y a absence d'unité de l'invention (suite du point 2 de la première feuille)**

L'administration chargée de la recherche internationale a trouvé plusieurs inventions dans la demande internationale, à savoir:

1. ☐ Comme toutes les taxes additionnelles ont été payées dans les délais par le déposant, le présent rapport de recherche internationale porte sur toutes les revendications pouvant faire l'objet d'une recherche.
2. ☐ Comme toutes les recherches portant sur les revendications qui s'y prétaient ont pu être effectuées sans effort particulier justifiant une taxe additionnelle, l'administration n'a sollicité le paiement d'aucune taxe de cette nature.
3. ☐ Comme une partie seulement des taxes additionnelles demandées a été payée dans les délais par le déposant, le présent rapport de recherche internationale ne porte que sur les revendications pour lesquelles les taxes ont été payées, à savoir les revendications n°
4. ☐ Aucune taxe additionnelle demandée n'a été payée dans les délais par le déposant. En conséquence, le présent rapport de recherche internationale ne porte que sur l'invention mentionnée en premier lieu dans les revendications; elle est couverte par les revendications n°

Remarque quant à la réserve

- ☐ Les taxes additionnelles étaient accompagnées d'une réserve de la part du déposant.
- ☐ Le paiement des taxes additionnelles n'était assorti d'aucune réserve.

SUITE DES RENSEIGNEMENTS INDICUES SUR PCT/ISA/ 210

Revendications recherchées partiellement: 1,2,5-8.  
A cause du grand nombre de composés, que définit théoriquement la formule générale de la revendication 1, la recherche a du être limitée pour des raisons économiques. La recherche a été restreinte aux composés mentionnés dans les revendications et pour lesquels des données pharmacologiques sont mentionnées et à l'idée générale de l'application.

# RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Dern: Internationale No  
PC./FR 98/02478

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)	Date de publication
GB 1584462 A	11-02-1981	BE 865468 A	02-10-1978
		CA 1091679 A	16-12-1980
		CH 628026 A	15-02-1982
		DE 2809625 A	05-10-1978
		DK 140878 A,B,	01-10-1978
		FR 2385693 A	27-10-1978
		IE 46566 B	27-07-1983
		JP 1400453 C	28-09-1987
		JP 53121724 A	24-10-1978
		JP 62009103 B	26-02-1987
		LU 79335 A	28-09-1978
		LU 90153 A	16-02-1998
		NL 7803432 A,C	03-10-1978
		US 4177290 A	04-12-1979